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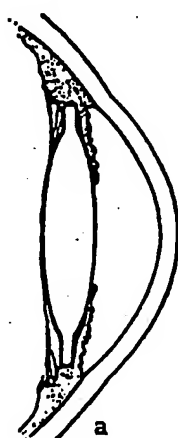
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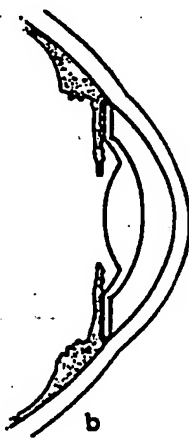
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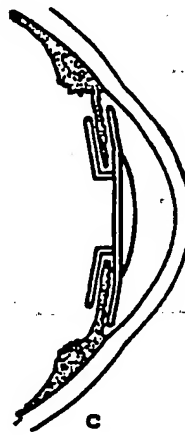
(54) Title: POLYURETHANE NETWORK FOR BIOMEDICAL USE



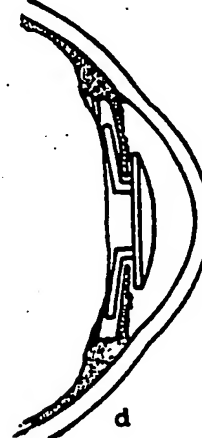
a: the Ridley lens



b: lens of the anterior chamber of the eye



c and d: iris-supported lenses



Examples of the shape for IOL

(57) Abstract

The invention relates to the use of a crosslinked polyurethane network in the biomedical field obtainable by reacting one or more low-molecular polyols having a functionality of three or more and one or more polyisocyanates having a functionality of two or more in the absence of a solvent, and to a number of specific uses of such polyurethane.

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Title: Polyurethane network for biomedical use

The invention relates to a densely crosslinked, glassy polyurethane network for biomedical uses.

Crosslinked polyurethanes are known, particularly as
5 rubberlike materials for use in the paint industry, car industry and in biomedical uses. Such polyurethanes possess good mechanical properties and can be processed in a reasonably simple manner.

The present invention is based on the development of a
10 new class of glassy crosslinked polyurethanes or polyurethane networks, prepared from low-molecular polyols in the absence of a solvent. Surprisingly, this yielded homogenous materials with good mechanical and optical properties, which can be used in the biomedical field.

15 Accordingly, the invention relates to a crosslinked polyurethane network for biomedical uses which can be obtained by reacting one or more low-molecular polyols having a functionality of three or more and one or more polyisocyanates having a functionality of two or more in the absence of a
20 solvent.

Such networks have a large number of uses in the biomedical field. Examples of such uses are intraocular lenses, keratoprotheses, composites with hydroxyapatite as
implants for hip joints or as tooth restoration material, and,
25 filled or not filled, as bone cement for fixing implants and fractures.

The preparation of the materials that are used according to the invention can be effected by reacting the starting components in the absence of a solvent. This yields homogenous
30 materials with good mechanical and optical properties, while the absence of a solvent obviously imposes restrictions on the selection of the starting substances. These starting substances should be miscible with each other and should have a low reactivity relative to each other. The amounts of the
35 starting components should be selected such that the number of hydroxyl groups and the number of isocyanate groups are

substantially equal, i.e., there should be a stoichiometric proportion. Preferably, the ratio of the amounts mentioned is between 0.95:1 and 1:1.05. More particularly, in biomedical uses it is preferred, for reasons of toxicity, not to use
5 excess quantities of isocyanate groups. During steam sterilization, any non-converted isocyanate groups that are present react to form allophanate linkages or amines.

To obtain suitable materials it is important that the polyols are low-molecular. In practice, this means that the
10 equivalent weight of the polyol is preferably maximally 125. In this case, by equivalent weight the molecular weight per hydroxyl group is meant. Generally, 3 or 4 functional polyols are started from, although higher functionalities can be used as well. Practically speaking, an upper limit lies at a
15 functionality of 8. However, it is also possible to include a minor amount of diols in the mixture. However, as diols do not give rise to crosslinking, it is required either to keep the amount thereof low or to work substantially with isocyanates having a functionality of 3 or more. Generally, the number of
20 hydroxyl groups originating from a diol will be less than approximately 10% of the total number of hydroxyl groups.

Preferred polyols are selected from the group consisting of triethanolamine (TEA), triisopropanolamine, 1,1,1-trimethylol-propane (TMP), N,N,N',N'-tetrakis (2-
25 hydroxypropyl)ethylenediamine (Quadrol), octakis (2-hydroxypropyl) pentaerythrityltetraamine, tetrakis(β -hydroxyethyl)methane, 1,1,1 trihydroxyethyl propane, 1,1,1 trihydroxyethylethane and other polyols. It is also possible to use a modified or unmodified pentaerythritol or inositol.

30 The polyisocyanates that can be used according to the invention are the conventional diisocyanates and higher isocyanates, for instance selected from the group consisting of butanediisocyanate, hexamethylene diisocyanate, dodecane diisocyanate, trans 1,4-cyclohexane diisocyanate, methylene
35 dicyclohexane diisocyanate, lysine di- or triisocyanate, isophoron diisocyanate, p-phenylene diisocyanate, methylene

diphenyl diisocyanate, triphenylmethanetriisocyanate, thiophosphoric acid tris(4-isocyanatiphenyl ester), polymeric methylene diphenyl diisocyanate, as well as trimerization products and adducts of these isocyanates, for instance on the basis of polyols. Examples of suitable polyols have been given hereinabove.

The selection of the polyol and the polyisocyanate substantially depends on the intended use. For uses wherein the color preservation of the material is important, it may be preferred to use aliphatic isocyanates. It is known that aromatic isocyanates may give rise to discolorization. In view of the use in the biomedical field, it may be preferred that the isocyanates and polyols be based on or related to so-called body-intrinsic substances. In that case, in particular butanediisocyanate and lysine-diisocyanate may be preferred. On the other hand, the very high degree of crosslinking of the materials usually lessens the necessity of working with body-intrinsic substances, because decomposition hardly occurs, if at all, so that no decomposition products can enter the body.

In the preparation of the polyurethanes it is preferred to start from pure and very dry starting substances, in an anhydrous environment. In the case where a stoichiometric or substantially stoichiometric proportion of the reactive components and a proper mixture thereof are used, the polyurethane is cured at a low temperature, after gelation optionally followed by curing above the glass transition temperature. In this manner, autoclavable materials are obtained. This may in particular be important in the case of materials to be implanted.

In particular cases, it is preferred to use a polyol obtained by alkoxylation of the corresponding amine. This has the advantage that the nitrogen of the amine compound functions as a catalyst for the polyurethane reaction, so that no separate catalyst need be added. In view of the applicability for medical uses, this is of course an important advantage. However, it is also possible to add a separate

catalyst that is suitable for forming polyurethane such as tin octoate or triethylamine.

The composition and the properties of the eventual material to a substantial extent depend on the intended use.

- 5 For many uses it is preferred to use a material whose glass transition temperature is at least 30°C. This glass transition temperature is measured on the dry, unswollen products.

- 10 Depending on the use of the material according to the invention, it is prepared in situ by reacting the starting components in the final shape, or the material is prepared separately and shaped through known shaping techniques such as milling or grinding.

- 15 During the manufacture of intraocular lenses the liquid resin can be poured into a mould and cured or milled from a block of the polyurethane. For implantation, the material can be sterilized by steam or for instance 120°C. Further, an important advantage is that during this sterilization by steam the network takes up water, so that the tolerance of the body of these materials is increased. Obviously, in the case of
20 intraocular lenses it is important that the material is optically clear, while it is also advantageous if it is hydrophilic or rendered hydrophilic by a coating of a polymer or a protein such as polyacrylamide or heparin. A reasonable strength is desired, so that damage to the lens during
25 implantation and use can be prevented. If so desired, the lens can be made UV-absorbing by admixing a UV-absorber:

- Preferably, for the implant a polyurethane is used with a maximum water uptake and a glass transition temperature of approximately 35°C. Suitable components for the manufacture
30 are, for instance, Quadrol, copolymers of triethanolamine with triisopropanolamine or Quadrol with hexamethylene diisocyanate. However, it is also possible to use lysinediisocyanate or butanediisocyanate, which is slightly preferred because of the relationship to substances in the
35 body.

When the materials according to the invention are used for implants or tooth restoration activities, it is desired to incorporate a filler into the network. A suitable filler is hydroxyapatite, which can be incorporated into the network in particularly large amounts. Therefore, the amount of hydroxyapatite is 25-95% by weight of the total composite consisting of network and hydroxyapatite. Hydroxyapatite has the important advantage that it is compatible with the body, while it also has a high modulus and a hardness and coefficient of expansion comparable with the human bone. Moreover, the use of hydroxyapatite in the polymeric network has the advantage that hydroxyapatite possesses reactive groups that react with isocyanates, so that a particularly good adhesion to the network is obtained.

When such composites are used as a hip implant, a good resistance to shock-loading and fatigue should be present, since the hip is to absorb a substantial force during walking, while, in view of the service life, the fatigue demands are quite heavy. If so desired, it is possible to incorporate a core of metal into the material. It is important that the composite possesses mechanical properties, such as rigidity at the interface, which correspond to the properties of the bone. Impact resistance, toughness, strength and fatigue strength should be maximal. By using materials according to the invention, a hip implant is obtained that is form stable and chemically stable during heating, so that it can be sterilized by steam, without being susceptible to biochemical decomposition by the body. When a highly filled polyurethane is used in the implant, preferably a high glass transition temperature and a low water uptake are used. As isocyanates, preferably the polyisocyanates on the basis of body-intrinsic substances are used.

The composites must satisfy yet other requirements when they are to be used for restoring teeth and molars. It is for instance important that the material is comparable with dental enamel in hardness and wear resistance, while possessing a

great strength, impact strength and fatigue strength, also in the environment in the mouth. Obviously, the color should be comparable with that of teeth, while the thermal expansion should also correspond to the thermal expansion of the teeth or molars. Of course, a proper adhesion of the restoration material is also required. The material according to the invention proves to have these properties to a high degree. An important advantage of the materials according to the present invention is that the mixture of polyol, polyisocyanate and filler can be cured in the mouth, for instance by heating or by using a local microwave radiation source. In general, the restoration material is obtained by mixing the two reaction components together, both filled with a suitable filler, such as hydroxyapatite. If so desired, the polyisocyanate may have been prepolymerized, so that the volatility and toxicity are decreased.

The material according to the invention can also be used in the case of bone fractures or for fixing implants. At present, this involves the use of a bone cement based on diacrylates or metals, or polylactic acid bone plates. However, on the basis of the present invention, a bone cement can be developed which is not poisonous and which, by admixing hydroxyapatite, promotes the growth of bone. According to a special embodiment of the invention, the hydroxyapatite to be used can be modified by a polyisocyanate so as to improve the adhesion to the hydroxyapatite and the wetting thereof with the resin. This modification can for instance be effected by mixing the hydroxyapatite with a polyisocyanate, such as HDI, and heating the mixture for some time.

Other uses according to the invention will be clear to the skilled person, and may for instance lie in the more conventional fields of application for polyurethane, such as glues for various components that are difficult to glue, and as matrix material for high-grade composites.

Also, various additives may be added to the material according to the invention. Examples thereof are, for

instance, the additives mentioned hereinabove and used in the examples, such as optically active materials and fillers. It is also possible to use fibers, for instance glass fibers, carbon fibers, polyethylene fibers or aramid fibers. As
5 optically active materials, for instance UV absorbers and optical intensifiers can be considered.

It also proves to be possible to use the materials according to the present invention within the framework of the manufacture of temperature resistant polymeric optical fibers.
10 By injecting low-viscosity resin into hollow fibers, an optical fiber having good optical properties in the visible-light spectrum is obtained.

The invention will be explained hereinafter on the basis of some examples, but is not limited thereto.

15

Example I, Intraocular lenses/keratoprosthesis

Material:

20 Quadrol, freshly vacuum-distilled and stored under nitrogen atmosphere. Hexamethylene diisocyanate (HDI), freshly vacuum-distilled and stored under nitrogen.

Process:

25

5 g of Quadrol was transferred under nitrogen into a dry three-necked flask. In the flask a bar stirrer with teflon stirring blade (wijnberg stirrer) is provided. 5.74 g (a stoichiometric amount) of HDI was added to the flask. The
30 components were stirred vigorously with the stirrer for approximately 15 minutes until the liquids changed into a clear and homogenous, yet still little viscous resin. To enable the discharge of reaction heat, the three-necked flask was disposed in a water bath of 20°C. After mixing, the resin
35 was degassed by tripple vacuum suction at low pressure (< 0.01 mbar) and flushing with nitrogen.

Shaping:

Depending on the temperature, the resin quickly became
5 viscous and started gelating 45 minutes after mixing. By
allowing the resin to gelate at room temperature in the flask
under nitrogen atmosphere for some days and subsequently
curing it for 3-20 hours in an oil bath at 90-120°C, a clear
and hard piece of polymer was formed. From this, the desired
10 shape for an intraocular lens and keratoprosthesis were
obtained by a cutting operation, in this case milling.

Prior to implantation, the lens was sterilized in steam
at 120°C for 20 minutes.

See Figs 1 and 2 for examples of the lens and
15 keratoprosthesis.

Properties:

The network had reacted completely to form a glassy and
20 clear material. The glass temperature was approximately 85°C,
no isocyanate groups could be detected by IR.

Mechanical properties:

25 At room temperature, the netted polyurethane was hard and
slightly brittle. The material had an elasticity modulus of 3
GPa, a tensile strength of 90 MPa at an elongation at break of
15%. A rise in temperature rendered the material less rigid
and brittle.

30

Water uptake:

The network took up 1% of water after autoclaving.
Consequently, the glass temperature decreased to 40°C.

35

Properties in the body:

5 Lenses and keratoprotheses were implanted in the eyes of chinchilla rabbits. The lenses were well tolerated and the cornea did not become clouded. Even one year after the operation, the cornea was still clear.

Example II

10 The process of Example I was repeated, while Coumarin 102 Laser dye was added to the resin for obtaining UV absorption.

Process:

15 As in Example I, but 2 per mille of Coumarin 102 were added to the Quadrol.

Properties:

20 The Coumarin absorbed UV light under 400 nm and gave the lens a blue-yellow fluorescent coloration. The other properties were not influenced.

Example III

25 The process of Example I was repeated, but after degassing a different method for shaping the intraocular lens (IOL) was used.

30 Shaping:

The other method for realizing an IOL is pouring the resin into a polished steel mold of the desired shape. In this manner, complex shapes can be obtained with a very high surface quality. To prevent adhesion to the mold, the mold was dried in an oven and provided with a surface coating. Pouring

35

out and curing in the mold took place in a glovebox with nitrogen atmosphere.

As surface coating, a Silicon solution in isopropanol Serva chem was used. After wetting, the silicon layer was
5 dried in air at 110°C for 2 hours.

Example IV

By pouring a resin according to the invention into a teflon
10 mould and removing it after curing, an article, for instance a cylindrical implant, can be made.

Material:

15 Quadrol, as in Example I
TEA freshly distilled and stored under N₂
HDI as I

Process:

20

As in I, but now the two alcohols are first mixed in the molar ratio of 80/20. In the flask 3.148 g of Quadrol were mixed with 0.551 g of TEA. After mixing, 4.548 g of HDI were
added.

25

Shaping:

The article was obtained by curing a resin in a mould.
The mixture was cured at room temperature for 1 day and
30 subsequently at 105°C in vacuum for 20 hours. After curing of the polyurethane, the article was removed from the mould.

Properties:

The polyurethane network had a glass temperature of 73°C, but after forced water uptake at 100°C the T_g decreased to
5 33°C.

Mechanical properties:

Important properties of the article were the lack of
10 creep. This material did not exhibit any creep at 20% deformation and above the T_g it had a modulus of 20 MPa. Other properties can be found in Tables 1 and 2.

Water uptake:

15

The network takes up 5% by weight of water.

Biocompatibility and durability:

20

Implantation of the articles in the abdomen of rats yielded highly encouraging results as far as tolerance and durability are concerned. Owing to the smooth surface, the articles were encapsulated only slightly (favorable), the mechanical properties were maintained and the weight remained
25 the same, i.e., hardly any degradation occurred, if at all.

Example V, Optical fibers

In the same manner as described in Example IV, a long
30 fiber could be made. In this connection, it is important that a proper adhesion is present between the mould (hose) and the core to prevent breaking losses. It is also crucial for the light conductivity that the refractive index of the cladding is lower than that of the core.

35

Material:

TMP, freshly vacuum-distilled from sodium
Dry and free of O₂

5 HDI as in I

Process:

As in Example I; the flask was disposed in an oil bath of
10 60°C. In this bath, 6.082 g of TMP were melted. Under vigorous
agitation, 12.7 g of HDI were added. The liquids do not mix.
Mixing took place only at 81°C. After stirring for 7 minutes,
the mixture was cooled down quickly to room temperature. The
TMP crystallized to form a white slurry. After heating to 81°C
15 and stirring for 3 minutes, the resin remained clear during
cooling down. Flask and resin were degassed at 80°C and 0.05
mbar for 5 minutes. After flushing three times with N₂/vacuum,
the resin was bubble-free and clear.

20 **Shaping:**

The resin was poured into a 15 ml syringe. In the same
manner as in Example IV, a teflon (TW20) hose with needle was
attached to this. The hose length is 5 meters. By means of a
25 bench screw, the viscous resin was forced into the hose. To
facilitate the flow of resin through the hose it was heated
somewhat with a hot-air blower. Curing took place at room
temperature and was followed by 2 hours of postcuring at 90°C
in a wind oven.

30

Properties:

The polyurethane network had a refractive index of 1.48.
Orienting tests demonstrated the optical conductivity of the
35 fiber. The light conductor of polyurethane/teflon of a fiber
length of 1 meter transmitted the light of a red LED with

hardly any weakening. The polyurethane of TMP/HDI has a very low degree of swelling ($< 1\%$) in water and is resistant to solvents. The glass temperature was 85°C . The mechanical properties were: tensile strength = 90 MPa, elongation at break 15%. Elasticity modulus = 3 GPa.

Example VI

In the same manner as described in Example I, a number of polyurethane networks were prepared using a number of different starting products in different ratios. The glass transition temperatures of these products were determined and included in the tables.

Table 1: thermal properties of the PU networks

5 Glass temperature homopolymers

	TIPA	Quadrol	octaol	TEA	BHEIPA	TMP
HDI	75	85	106	33	45	83
LDI	-	72	-	34	-	-
IPDI	160	165	-	133	-	184
tCHDI	178	190	-	125	-	227

Glass temperature copolymers

Material mole % Quadrol/TEA	Tg °C	Tg after water uptake °C
0/100	32	-10
80/20	73	33
60/40	70	23

10

Table 2: mechanical properties of the PU networks

Code	Material mole % Quadrol/ TEA	σ_b T>Tg MPa	E_{mod} T>Tg MPa	ϵ_b T>Tg %	T T>Tg MPa	σ_b (H ₂ O) 40°C MPa	E_{mod} (H ₂ O) 40°C MPa	ϵ_b (H ₂ O) 40°C %	T (H ₂ O) 40°C MPa
TH100	0/100	14.2	17.4	94	3.1	3.1	15.3	73	-
TH110	80/20	9.8	21.4	50	2.4	-	-	-	-
TH118	60/40	9.6	21.4	50	2.3	17.3	57.0	82	7.5

15

Example VII

14.5 g of a fraction < 0.05 mm of synthetic hydroxyapatite, sintered and ground, were dried and inserted into a three-neck flask, followed by stirring at 100°C under vacuum for 1 hour. Subsequently, it was cooled with liquid nitrogen and a large excess quantity of HDI was distilled into the flask. The resulting suspension was heated to room temperature and subsequently the flask was gassed with nitrogen. The suspension was heated to 90°C, after which it was stirred for another two hours. By distillation at 90°C under high vacuum the excess quantity of HDI was removed.

The resulting product is a dry, free-flowing powder containing 5% by weight of bound HDI, which could not be removed by washing with chloroform. IR analysis showed that approximately half the isocyanate groups had reacted.

5 ml of Quadrol was added to the thus obtained pretreated hydroxyapatite. The mixture was heated under vacuum to 90°C, after which it was stirred under 1 bar nitrogen for 2 hours. In a glovebox filled with CO₂- and H₂O-free nitrogen, an equivalent amount of HDI was added to the mixture. Under vigorous agitation with a pestle in a mortar, a homogenous, white resin was obtained. After degassing three times under vacuum, the resin was injected into a PTFE hose and cured by means of IR radiation.

The resulting material had the following properties:

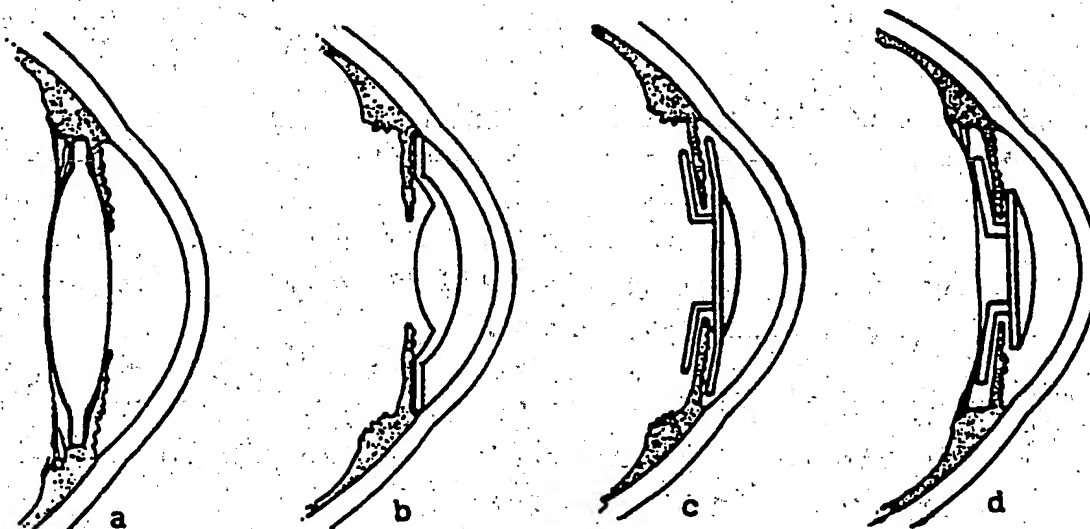
Tensile strength	110 MPa
Modulus	6 GPa
Tg	82°C
HAp content	57%
Water uptake (35°C)	3%

These values show that the material is suitable for use as tooth restoration material or bone cement.

CLAIMS

1. The use of a crosslinked polyurethane network in the biomedical field obtainable by reacting one or more low-molecular polyols having a functionality of three or more and one or more polyisocyanates having a functionality of two or more in the absence of a solvent.
2. The use according to claim 1, wherein the starting materials are selected such that the glass transition temperature is at least 30°C.
3. The use according to claim 1 or 2, wherein the starting materials are selected such that the network is completely or substantially completely homogenous.
4. The use according to claims 1-3, wherein the number of hydroxyl groups and the number of isocyanate groups are substantially equal.
5. The use according to claims 1-4, wherein the equivalent weight of the polyol is maximally 125.
6. The use according to claims 1-5, wherein as polyol at least one compound is used selected from the group consisting of triethanolamine, triisopropanolamine, 1,1,1-trimethylolpropane, N,N,N',N'-tetrakis (2-hydroxypropyl)-ethylenediamine, threitol, octakis (2-hydroxypropyl) and pentaerythrityltetraamine, tetrakis(β -hydroxyethyl)methane, 1,1,1 trihydroxyethyl propane and 1,1,1 trihydroxyethylethane.
7. The use according to claims 1-6, wherein as polyisocyanate at least one compound is used from the group consisting of butanediisocyanate, hexamethylene diisocyanate, dodecane diisocyanate, trans 1,4-cyclohexane diisocyanate, methylene dicyclohexane diisocyanate, lysine di- or triisocyanate, isophoron diisocyanate, p-phenylene diisocyanate, methylene diphenyl diisocyanate, triphenylmethanetriisocyanate, thiophosphoric acid tris(4-isocyanatiphenyl ester), polymeric methylene diphenyl diisocyanate, as well as trimerization products and adducts of said isocyanates.

8. The use according to claims 1-7, wherein the degree of swelling is 200% at the most.
9. A polyurethane composite comprising a polyurethane as defined in claims 1-8 and a filler, for instance modified or unmodified hydroxyapatite.
10. The use of a polyurethane or polyurethane composite, optionally provided with a hydrophilic coating, according to claims 1-8 as biomedical material.
11. An intraocular lens manufactured from a polyurethane as defined in claims 1-8.
12. An implant for joints manufactured from the polyurethane composite according to claim 9.
13. The use of a polyurethane composite according to claim 9 as bone cement or tooth restoration material.
14. A process for preparing a crosslinked polyurethane network suitable for biomedical uses by reacting one or more low-molecular polyols having a functionality of three or more and one or more polyisocyanates having a functionality of two or more in the absence of a solvent.
15. A process according to claim 14, comprising the mixing of the pure components, followed by curing said components at low temperature, preferably by microwave radiation.
16. A process according to claim 14 or 15, comprising the mixing of the pure components, followed by curing said components at a temperature above the glass transition temperature of the polyurethane.



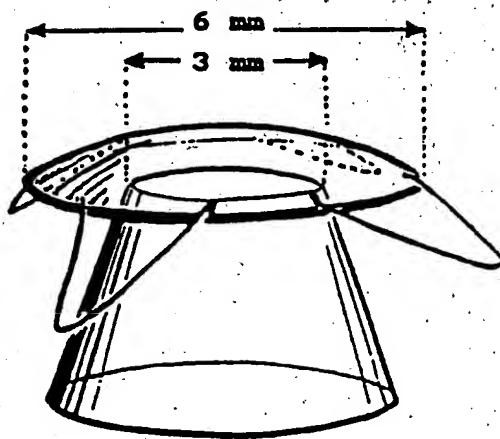
a: the Ridley lens

b: lens of the anterior chamber of the eye

c and d: iris-supported lenses

Examples of the shape for IOL

FIG. 1



Example keratoprosthesis

FIG. 2

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/NL 93/00203

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C08G18/32 A61L27/00 A61L31/00 A61F2/14 G02B1/04
G02B6/16 B29D11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C08G A61L G02B C09J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR,A,2 540 878 (HEXCEL-FRANCE) 17 August 1984 see claims 1-5 see page 1, line 19 - page 2, line 26	14, 15
X	EP,A,0 022 215 (BAYER) 14 January 1981 see claim 1 see page 5, paragraph 2 see page 9, paragraph 2 - paragraph 4	14, 16
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☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

Inter. Application No

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